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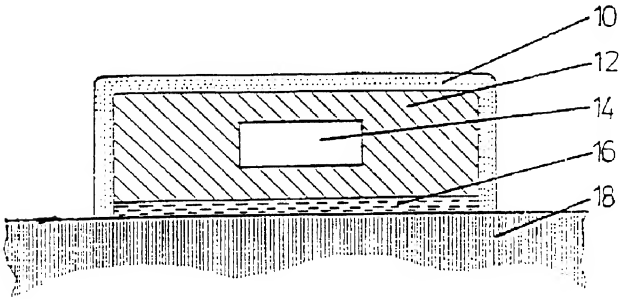
(54) Titre : SYSTEME TRANSDERMIQUE THERAPEUTIQUE ET SON PROCEDE DE PRODUCTION
(54) Title: TRANSDERMAL THERAPEUTIC SYSTEM AND PROCESS FOR ITS PRODUCTION



(57) Abrégé/Abstract:
The invention relates to a transdermal therapy system (TTS) which comprises the following essential characteristics: a back layer which faces away from the skin and is impermeable to the active agent, at least one active agent deposit, a matrix which is connected to said active agent deposit and which controls the release of the active agent; and an adhesive fixing device for fixing the therapy system on the skin. The deposit and/or the matrix also contain support materials consisting of paper. The invention also relates to a method for producing the inventive transdermal therapy system and to the use of the same.

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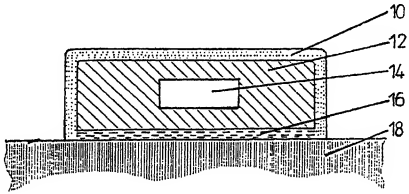
(54) Title: TRANSDERMAL THERAPY SYSTEM AND METHOD FOR PRODUCING THE SAME

(54) Bezeichnung: TRANSDERMALES THERAPEUTISCHES SYSTEM UND VERFAHREN ZU SEINER HERSTELLUNG



(57) Abstract

The invention relates to a transdermal therapy system (TTS) which comprises the following essential characteristics: a back layer which faces away from the skin and is impermeable to the active agent, at least one active agent deposit, a matrix which is connected to said active agent deposit and which controls the release of the active agent; and an adhesive fixing device for fixing the therapy system on the skin. The deposit and/or the matrix also contain support materials consisting of paper. The invention also relates to a method for producing the inventive transdermal therapy system and to the use of the same.

(57) Zusammenfassung

Die Erfindung betrifft ein transdermales therapeutisches System (TTS), das als wesentliche Merkmale eine der Haut abgewandte, für den Wirkstoff undurchlässige Rückschicht, mindestens ein Wirkstoffdepot, eine Matrix, die mit dem Wirkstoffdepot in Verbindung steht und die Abgabe des Wirkstoffs steuert, und eine haftklebende Fixierungseinrichtung für das therapeutische System auf der Haut enthält, wobei das Depot und/oder die Matrix noch Stützmaterialien aus Papier enthalten. Die Erfindung betrifft weiterhin ein Verfahren zu dessen Herstellung und dessen Verwendung.

LEDIGLICH ZUR INFORMATION

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Transdermal Therapeutic System and Process for its Production

Specification

The invention relates to a transdermal therapeutic system (TTS) and a process for its production.

Therapeutic systems for the transdermal administration of pharmaceuticals, such as nicotine, nitroglycerine, sexual hormones, scopolamine, fentanyl are known. Suitable systems have for example been described in international application DE 87/00372 (WO 88/01516). Such systems contain as essential features a backing layer which is remote from the skin and impermeable for the active substance, at least one active substance depot, an active substance distribution device which is in contact with the active substance depot, a control device which controls the delivery of the active substance by the system, and a pressure-sensitive adhesive fixing device for the therapeutic system on the skin. The active substance distribution device may be combined with the control device to yield a reservoir matrix which has one or more discrete active substance depots arranged in spatially defined manner with respect to one another and having a higher active substance concentration than that which is present in the reservoir matrix.

It is stated in WO 88/01516 that the depot may also contain inert adjuvants such as support materials which make the active substance depot insensitive with respect to application of pressure and tension, and carriers. According to US patent specification 5,820,876 the support material may be a planar fabric (support fabric) as an inert adjuvant, by which the distribution of the active substance within the depot is effected and favored. A particular embodiment is also disclosed in Figure 5 of both documents, according to which an adhesive layer is provided on a backing layer, upon which the active substance is present, if desired with adjuvants, such as material for facilitating the processability of the active substance, or carrier materials such as fabrics. The support fabric may also be present as a non-woven fabric (fleece). In the examples fleece materials are disclosed as being suitable (50:50 viscose rayon-cotton fiber blend with a substance weight of 80 g/m², Paratex II/80 of the company Lohmann GmbH & Co. KG, or a 70:30 viscose rayon-cotton fiber blend with a substance weight of 40 g/m², Paratex III/40 of the company Lohmann GmbH & Co. KG). In both examples it is additionally stated that the fleece material acts as a support fabric and also to assist the uniform distribution of the nicotine, as an inert adjuvant as defined in the introductory part of the specification.

US patent specification 4,597,961 discloses a different form of a transdermal therapeutic system. In this system the delivery of the active substance is generally controlled by a microporous membrane. It is stated in the description of Figure 2 that reservoir 114 can contain a suitable absorbent material 122, such as a sponge or cotton, on which is absorbed the desired quantity of liquid nicotine. Additionally it is pointed out in Example 4 that reservoir 114 contains a dense matrix of inert fibrous or porous material, such as cotton, to prevent loss of nicotine. The term "matrix" is used in this context however for a completely different technical feature than in WO 88/01516 and US patent specification 5,820,876.

There is further known a TTS for nicotine from US patent specification 4,915,950, in which a depot layer (13) is arranged between an adhesive (14), acting as a control device, and an anchoring adhesive (12). The active substance depot layer may consist of a non-woven fabric (fleece) e.g. polyester, polyethylene, polypropylene, polyamides, rayon or cotton and may particularly consist of a 100% polyester non-woven. There is no disclosure or hint at all of the use of paper in or by this specification.

It has now been found that a TTS with a quality substantially improved compared with the known state of the art is obtained if instead of the known support materials, including particularly fabrics such as fleece, the carrier material is paper. Paper is distinguished fundamentally from fabrics including non-woven (fleece) by the fact that in it the cellulose fibers are joined to form a thin layer by strengthening. The cohesion of the fibers in the paper is effected - besides the mechanical adherence and the hooking-together of the fibers - by chemical bonds (hydrogen bonds) which are formed between the hydroxyl groups of the cellulose molecules in the course of the manufacture of the paper. This chemical bond is so strong that the tensile strength of paper can even exceed that of ordinary construction steel (RM Consult Papiermaschinen Info – http: //home.t-online.de/home/rm.consult/rm-info.htm of November 17, 1998). In addition, paper has the advantage that it has a high absorption capacity for liquid phases which is characterized by DIN ISO 8787 by the height of suction.Thus the height of suction in the long direction determined for paper with a basis weight of 26 g/m^2 was 146 mm/10 min and in cross direction 143 mm/10 min compared with values of about 110 and 80 mm/10 min for the abovementioned fleece material Paratex III/40, where the values for the fleece varied to a very large extent in the serial tests. Paper ordinarily does not contain a binding agent, so that no incompatibilities can occur between active substance and binding agent.

Subject of the invention therefore is a transdermal therapeutic system containing as essential features

a) a backing layer remote from the skin and impermeable for the active substance,

b) at least one active substance depot,

c) a matrix contacting the active substance depot and controlling the delivery of the active substance, and

d) a pressure-sensitive adhesive fixing device for the therapeutic system on the skin, the depot or the matrix or both containing support materials, wherein the support material consists of paper.

In one product aspect, the invention provides a transdermal therapeutic system, comprising: (a) a backing layer remote from the skin and impermeable for an active substance; (b) at least one active substance depot; (c) a matrix containing the active substance depot and controlling the delivery of the active substance; and (d) a pressure-sensitive adhesive fixing device for the therapeutic system on the skin, wherein the depot, the matrix or both contain a support material, wherein the support material consists of paper and the active substance is lidocaine, diphenylhydramine hydrochloride, salbutamol, 5-fluorouracil, one or more sexual horomones or gestagens, or fentanyl.

In one process aspect, the invention provides a process for the production of the transdermal therapeutic system as defined above, wherein: (i) a pressure-sensitive adhesive composition is applied to a dehesively finished protective layer (A) such that after the evaporation of solvents a pressure-sensitive layer is

formed; (ii) an adhesive composition is applied to a further dehesively finished protective layer (B) such that after evaporation of solvent a film is produced, and the film is laminated to the pressure-sensitive adhesive layer applied to the protective layer (A) forming a lower sheet; (iii) in a further coating step an adhesive composition is applied to a further dehesively finished protective layer (C) such that after evaporation of solvents a film is produced upon which the backing layer impermeable for the active substance is laminated forming an upper sheet; (iv) after removal of the dehesively finished protective layer (B) from the lower sheet there are positioned centrally disks, made of paper; (v) subsequently the active substance is dosed onto the disks of paper by means of a tampon; and (vi) after removal of the dehesively finished protective layer (C) the upper sheet is laminated to the lower sheet and the transdermal therapeutic systems are punched therefrom.

Using paper as support material and inert adjuvant according to the invention has various advantages. When using fabrics, such as fleeces, there is always a certain range of deviation of the amount of active substance transferred to the single TTS, this being so in spite of a good dosing technique. For example, it has been observed that the amounts of nicotine transferred to the single TTS have a range of deviation of about 4% when using a fleece (70:30 viscose-cotton fiber blend, substance weight 40 g/m²). If according to the invention paper is used instead, the range of deviation is considerably smaller; dependent on the surface weight of the paper it is significantly below 2%, e.g. with a paper having a basis weight of 23 g/m² below 1.9% and with paper having a basis weight of 26 g/m² even below 1.2%. The preferred papers have a basis weight of from 9 to 60, preferably from 15 to 40 and particularly from 20 to 35 g/m².

The use of paper as support material in TTS according to the invention is, however, of importance not only for the uniformity of the TTS produced but also for the production technique. According to a known process a defined amount of the active substance is transferred to the support material by means of a tampon. This implies that in this process a certain amount of the support material is rubbed off by the tampon and is entrained upon detaching of the tampon from the support material. This requires the tampon to be cleaned at certain intervals and thus the production process has to be interrupted. When using paper according to the invention the abrasion is significantly reduced, which can be explained by the fact that the fibers of paper are more firmly joined with each other than for example the fibers in a fleece or other fabric. It is known that fibrous fractions emanate from every fabric. It is made possible by the use of paper according to the invention that the ability of the tampon to function is prolonged at least by 10 times, mostly even by 50 to 100 times, so that

its cleaning and accordingly an interruption of the production process are required much less frequently.

TTS according to the invention can be of various configurations. Suitable embodiments are shown in the attached Figures 1 and 2, although other embodiments are possible, as they are for example disclosed in international application WO 88/01516. According to Figures 1 and 2 the TTS consist of a backing layer (10), a reservoir matrix (12), one or more depots (14) and a fixing device (16) which are provided with a protective foil which is removed before administration so that the system is then fixed on the skin (18). The protective foil has also to be impermeable for the active substance, of course.

For the backing layer, the reservoir matrix, the fixing device and the protective foils, materials known to the skilled worker are used.

Subject of the invention is also a process for the improved production of transdermal therapeutic systems with a reduced range of deviation of the amounts of active substance applied, wherein the active substance is applied in conventional manner by means of a tampon to a support material which consists of paper. According to a preferred embodiment the deviation (relative standard deviation) of the amount of active substance applied, as achieved by the procedure of the invention, is less than 2%, particularly below 1.2%.

A final subject of the invention consists in the use of paper as a support and distribution medium in transdermal therapeutic systems.

The systems according to the invention are in principle suitable for all active substances which can be administered transdermally. Particularly there may be named, in addition to those mentioned above, lidocaine, diphenylhydramine hydrochloride, salbutamol, 5-fluorouracil and as sexual hormone estradiol and also gestagens such as norethindrone acetate, levonorgestrel.

Example 1

First a pressure-sensitive adhesive preparation HS is prepared by homogenizing

a) 933 g of a commercial product (®Durotak 387-2516 of the company National Starch and Chemical, Zutphen, the Netherlands– this is a 40% solution of a self-crosslinking acrylate polymer based on 2-ethylhexyl acrylate, vinyl acetate, acrylic

acid and titanium chelate ester in a solvent mixture of ethyl acetate, ethanol, heptane and methanol) with

b) 8 g of a triglyceride of fractionated coconut fatty acids (C_8-C_{10}; ®Miglyol 812 of the company Hüls AG, Witten, Germany).

In addition 6210 g of ®Durotak 387-2516, 553 g of ethyl acetate and 311 g of ethanol are combined with 66 g of the aforementioned triglyceride and with 626 g of an acrylic resin prepared from dimethylaminoethyl methacrylate and neutral methacrylic acid esters (®Eudragit E 100 of the company Röhm-Pharma, Darmstadt, Germany) and homogenized (adhesive composition MS).

In addition 72 g of ®Eudragit E 100 are introduced into 101 g nicotine and dissolved therein. Thus the active substance preparation is obtained.

The pressure-sensitive adhesive composition HS is applied to a dehesively finished protective layer (A) such that after the evaporation of the solvents a pressure-sensitive adhesive layer is formed with a substance weight of 40 g/m².

The adhesive composition MS is applied to a further dehesively finished protective layer (B) such that after evaporation of the solvents a film having a substance weight of 220 g/m² is produced. Ths film is laminated to the pressure-sensitive adhesive layer applied to the protective layer (A). Thus the lower sheet is obtained.

In a further coating step the adhesive composition MS is applied to a further dehesively finished protective layer (C) such that after evaporation of the solvents a film having a substance weight of 110 g/m² is produced upon which the backing layer impermeable for the active substance is laminated. Here the upper sheet is produced.

After removal of the dehesively finished protective layer (B) from the lower sheet there are positioned centrally disks made of a fleece fabric (70:30 viscose rayon-cotton fiber blend- substance weight 40 g/m²) or paper (26 or 24 g/m² respectively).

Subsequently the active substance preparation is dosed onto the disks of fleece material or paper, respectively.

After removal of the dehesively finished protective layer (C) the upper sheet is laminated to the lower sheet (finished with disks of fleece material or paper and

provided with active substance preparation), and transdermal therapeutic systems are punched therefrom. The results are evident from the following table:

Number of	*Cleaning of the Tampon*	
TTS produced	*Fleece material*	*Paper*
1,200	necessary	no
2,400	necessary again	no
3,600	necessary again	no
4,800	necessary again	no
more than 100,000	(continually after every 1,200 TTS)	no

As is evident from the table it is possible when using fleece material to produce only 1,200 transdermal therepeutic systems. Then cleaning of the device for transfer of the active substance (tampon) is required. Contrary thereto more than 100,000 transdermal therapeutic systems can be produced when using paper, without the need to shut down the machinery owing to cleaning becoming necessary.

Example 2

Transdermal therapeutic systems were produced according to Example 1 and the accuracy of the dosing was determined.

The amount of nicotine contained in the single transdermal therapeutic systems was determined and the results statistically evaluated. It was found that transdermal therapeutic systems which have been produced by using paper have a significantly smaller relative standard deviation (S-rel(%)) (see Figure 3).

CLAIMS:

1. A transdermal therapeutic system, comprising:

(a) a backing layer remote from the skin and impermeable for an active substance;

(b) at least one active substance depot;

(c) a matrix containing the active substance depot and controlling the delivery of the active substance; and

(d) a pressure-sensitive adhesive fixing device for the therapeutic system on the skin,

wherein the depot, the matrix or both contain a support material, wherein the support material consists of paper and the active substance is lidocaine, diphenylhydramine hydrochloride, salbutamol, 5-fluorouracil, one or more sexual horomones or gestagens, or fentanyl.

2. The transdermal therapeutic system as claimed in claim 1, wherein the active substance is estradiol, norethindrone acetate or levonorgestrel.

3. The transdermal therapeutic system as claimed in claim 1 or 2, wherein the paper has a basis weight of from 9 to 60 g/m^2.

4. The transdermal therapeutic system as claimed in claim 3, wherein the basis weight is from 15 to 40 g/m^2.

5. The transdermal therapeutic system as claimed in claim 4, wherein the basis weight is from 20 to 35 g/m^2.

6. A process for the production of the transdermal therapeutic system as defined in claim 1, wherein:

(i) a pressure-sensitive adhesive composition is applied to a dehesively finished protective layer (A) such that after the evaporation of solvents a pressure-sensitive layer is formed;

(ii) an adhesive composition is applied to a further dehesively finished protective layer (B) such that after evaporation of solvent a film is produced, and the film is laminated to the pressure-sensitive adhesive layer applied to the protective layer (A) forming a lower sheet;

(iii) in a further coating step an adhesive composition is applied to a further dehesively finished protective layer (C) such that after evaporation of solvents a film is produced upon which the backing layer impermeable for the active substance is laminated forming an upper sheet;

(iv) after removal of the dehesively finished protective layer (B) from the lower sheet there are positioned centrally disks, made of paper;

(v) subsequently the active substance is dosed onto the disks of paper by means of a tampon; and

(vi) after removal of the dehesively finished protective layer (C) the upper sheet is laminated to the lower sheet and the transdermal therapeutic systems are punched therefrom.

7. The process as claimed in claim 6, wherein the deviation of the amount of active substance applied is less than 2%.

8. The process as claimed in claim 7, wherein the deviation of the amount of active substance applied is less than 1.2%.

9. The process as claimed in any one of claims 6 to 8, wherein the paper has a basis weight as defined in any one of claims 3 to 5.

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PATENT AGENTS

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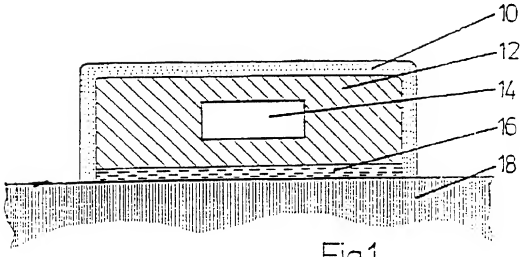


Fig.1

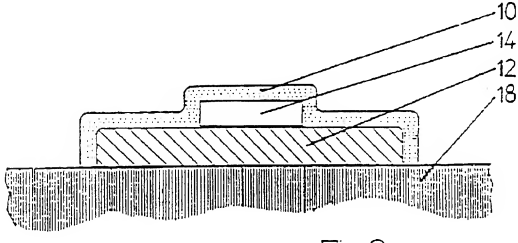
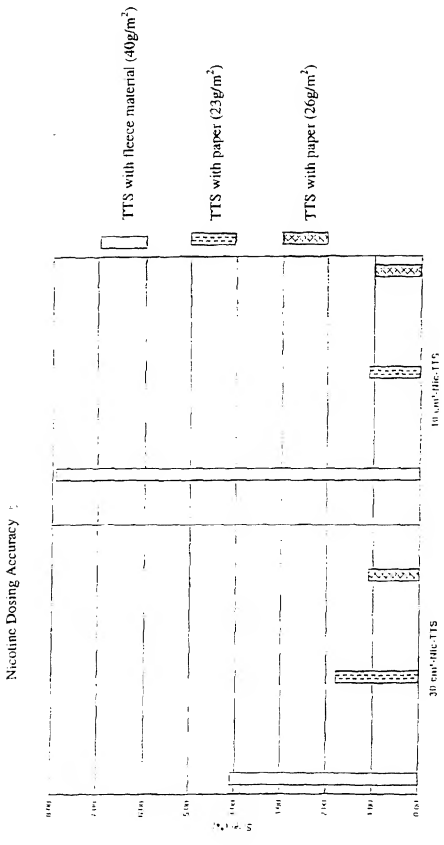


Fig.2

Figure 3


TTS with fleece material (40g/m²)
TTS with paper (23g/m²)
TTS with paper (26g/m²)
Nicotine Dosing Accuracy
30 cm²-Hic-TTS